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Saphenous Vein Graft Stenting and Major Adverse Cardiac Events
A Predictive Model Derived From a Pooled Analysis of 3958 Patients

Alanna Coolong, MD, MSc; Donald S. Baim, MD; Richard E. Kuntz, MD, MSc; A. James O’Malley, PhD; Sachin Marulkar, MBBS, MPH; Donald E. Cutlip, MD; Jeffrey J. Popma, MD; Laura Mauri, MD, MSc

Background—Treatment of saphenous vein graft (SVG) stenosis with percutaneous coronary intervention has a 15% to 20% incidence of major adverse cardiac events (MACE) within 30 days. Although MACE rates are reduced significantly by the use of embolic protection devices (EPDs), neither the level of baseline risk nor the benefit provided by EPDs has been well characterized.

Methods and Results—Data from 5 randomized controlled trials and 1 registry evaluating EPDs in SVG percutaneous coronary intervention (n=3958 patients) were pooled for analysis. MACE was defined as a composite of death, myocardial infarction, and target vessel revascularization. Baseline variables and 2 summary angiographic variables (an SVG degeneration score and an estimate of lesion plaque volume) were included in a multivariable logistic regression model to predict 30-day MACE, with adjustment for the type of device used and inter-study variation. The angiographic variables were potent predictors of MACE (increasing SVG degeneration score, P<0.0001; larger estimated plaque volume, P<0.0001), with significant contributions from the presence of thrombus (P<0.01), increasing patient age (P<0.01), glycoprotein IIb/IIIa inhibitor use (P=0.02), and current tobacco abuse (P=0.03). The treatment benefit of EPDs was preserved across all categories of risk as categorized by SVG degeneration or plaque volume.

Conclusions—The strongest predictors of 30-day MACE in SVG percutaneous coronary intervention are angiographic estimates of plaque volume and SVG degeneration. Identification of these predictors of 30-day MACE allows reliable prediction of patient outcomes and confirms consistent treatment benefit with the use of EPDs across the range of patients tested in randomized trials. (Circulation. 2008;117:790-797.)

Key Words: bypass stents

Saphenous venous bypass grafts have a progressive closure rate, estimated to be 12% to 20% at the end of the first year and ≈50% by 10 years.¹ Late (>1 year) occlusion of saphenous vein grafts (SVGs) is due predominantly to atherosclerotic degeneration as the thin-walled venous structure is devascularized and exposed to the higher wall stress associated with arterial pressure.² Reoperation carries substantially increased morbidity and mortality rates,³ making SVG percutaneous coronary intervention (PCI), in particular stent placement,⁴,⁵ a more attractive means of revascularization. However, SVG PCI is limited by a substantial risk of major adverse cardiac events (MACE) caused primarily by peri-procedural myocardial infarction (MI) as the result of no-reflow and distal embolization. Moreover, large MI (creatine kinase-MB >5 times normal) is predictive of late mortality in this patient population.⁶ The randomized, controlled Saphenous Vein Graft Angioplasty Free of Emboli (SAFER) trial of the first (distal occlusion) embolic protection device (GuardWire, Medtronic Vascular, Santa Rosa, Calif) in SVG PCI demonstrated a 42% reduction in 30-day MACE compared with the use of a conventional guidewire,⁷ supporting Food and Drug Administration (FDA) approval. The EPI FilterWire (Boston Scientific, Natick, Mass) demonstrated noninferiority to the GuardWire in the FilterWire EX Randomized Evaluation (FIRE),⁸ and several subsequent trials have demonstrated noninferiority of other embolic protection devices (EPDs) to the GuardWire or FilterWire.⁹–¹¹

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Despite the dramatic reduction in periprocedural morbidity associated with the use of these EPDs during SVG interven-
tion in these trials, it is estimated that EPDs are used in only half of SVG PCIs.12 In some cases, lesion location is not favorable for particular device types,13 but in other cases, operators may have the perception that some SVGs (eg, those with relative focal or smooth lesions) have a low enough risk to make use of an EPD unnecessary.12

We have previously reported that 2 angiographic variables (the percent of the SVG length with angiographic evidence of degeneration and the estimated volume of plaque in the stented lesion) were strong multivariable predictors of procedural risk within the first 801-patient SAFER study and could define subgroups whose risk without embolic protection varied from 4% to nearly 50%.14 Since the SAFER trial, a range of new devices (distal balloon occlusion, distal filter, proximal occlusion) has been evaluated in clinical trials that have randomized >3000 additional subjects. The determinants of adverse events across different EPDs, however, have not been determined, nor have the unique angiographic predictors from SAFER been validated on an independent data set. We therefore sought to analyze clinical and angiographic predictors of MACE after SVG PCI in this larger, broader population and to determine the pattern of treatment benefits of embolic protection across various risk strata.

**Methods**

**Study Population**

The Harvard Clinical Research Institute EPD data set consists of a total of 3992 patients with 4314 lesions enrolled in 5 randomized trials and 1 registry of EPDs for use during SVG PCI (Table 1). Thirty-day clinical outcomes were available for 3958 patients (99%) who made up the cohort used for this patient-based analysis. The study protocols and end-point definitions have been described previously and are similar across all studies.7-8,10-11,15,16 Eligible patients were those undergoing elective PCI of an SVG containing ≥50% diameter stenosis with no evidence of recent MI and a left ventricular ejection fraction ≥25%. MACE was defined in all trials as a 30-day composite of death, MI (defined as creatine kinase-MB elevation >3 times normal), or target vessel revascularization. Patients requiring adjunctive atherectomy or debulking procedures were excluded. An independent clinical events committee at the Harvard Clinical Research Institute adjudicated all adverse clinical events, and quantitative coronary angiography was performed at an independent core laboratory (Brigham and Women’s Hospital Angiographic Core Laboratory) using standardized methodology17 for all studies.

We examined a broad range of candidate clinical, angiographic, and procedural variables as possible predictors of MACE. Clinical variables included patient age; sex; current smoking; history of hypertension, hyperlipidemia, or prior MI; and vein graft age. Angiographic variables included lesion length (“shoulder to shoulder” >20% lumen narrowing), evidence of thrombus, vessel angioplasty >50%, and the 2 novel angiographic parameters (estimated plaque volume and SVG degeneration score) developed previously in the analysis of the SAFER trial.14 The reference vessel diameter (RVD) and minimum lumen diameter (MLD) were determined from 2 projections with an automated edge-detection algorithm (CMS Medical, Leiden, the Netherlands).18 Estimated plaque volume was defined as follows: \( \pi \text{lesion length} \times \left( \frac{\text{RVD}}{2} \right)^2 - \left( \frac{\text{MLD}}{2} \right)^2 \). This variable equals the volume of a cylinder with a diameter equal to the RVD and a length equal to lesion length minus the volume of a cylinder of the same length with a diameter equal to the MLD within the lesion (Figure 1). SVG degeneration score is an ordinal metric of the extent of lumen irregularities and ectasia (>20% of the reference normal segment) within the SVG that makes up <25% (SVG degeneration score, 0), 26% to 50% (SVG degeneration score, 1), 51% to 75% (SVG degeneration score, 2), or >75% (SVG degeneration score, 3) of the total SVG length (Figure 2). Procedural

<table>
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<tr>
<th>Trial</th>
<th>Year</th>
<th>Device Type</th>
<th>Patients, n</th>
<th>RVD Range, mm</th>
<th>30-Day MACE, %</th>
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<td>406</td>
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<td>2.8–6.2</td>
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CAPTIVE indicates CardioShield Application Protects During Transluminal Intervention of Vein Grafts by Reducing Emboli Trial; PROXIMAL, Proximal Protection During Saphenous Vein Graft Intervention Using the Proxis Embolic Protection System Trial; SPIDER, Saphenous Vein Graft Protection in a Distal Embolic Protection Randomized Trial; and BLAZE, Embolic Protection Transluminally With the FilterWire EZ Small Device in Saphenous Vein Grafts.

*Patients enrolled in superiority trial with associated probability values.
†Patients enrolled in noninferiority trial with associated probability values.
‡Registry.
§3958 patients available for analysis.
variables included both the planned (assessed before the procedure) and actual (assessed after the procedure) use of a glycoprotein IIb/IIIa inhibitor. Because these 2 procedural variables are highly correlated, actual glycoprotein IIb/IIIa inhibitor use was selected as the more clinically relevant variable for inclusion in the multivariable model.

We adjusted for the type of EPD used (compared with conventional guidewire use) to account for possible variation between devices, even though there were no statistically significant differences across EPDs.

Statistical Analyses
Univariate logistic regression analysis was performed for each of the candidate clinical, angiographic, and procedural variables to assess their relationship with the outcome of 30-day MACE. A correlation matrix was generated using each of the candidate variables to assess multicollinearity. Multivariable logistic regression analysis was performed using all of the angiographic, clinical, and procedural predictors with 30-day MACE as the outcome. Missing values were addressed by allowing the sample size to float, resulting in 3553 patients (90%) with complete data on all variables in the final multivariable model. The plaque volume component terms, lesion length, MLD, and RVD, were entered into the model as a group in the multivariable analysis, and the results were compared with the results when the summary predictor, estimated plaque volume, was in the model. The interaction between glycoprotein IIb/IIIa inhibitor and device type was examined. Predictors of planned and actual glycoprotein IIb/IIIa inhibitor use were evaluated. A 2-sided significance level of 0.05 was used. Results are presented as odds ratios with 95% confidence intervals.

Bayesian Analysis of Between-Study Variation
An analysis that pools information across studies is susceptible to bias introduced by unmeasured confounding variables (variables that predict treatment received and the outcome). To establish the potential for unmeasured confounding variables to influence the results of the analyses, we used a Bayesian hierarchical model to estimate the interstudy correlation coefficient, the ratio of the variation between studies to total variation. Very small values of the interstudy correlation coefficient indicate that the results are minimally susceptible to unmeasured confounding variables because there is little heterogeneity between studies.

To further check the legitimacy of pooling information across studies, the model was refitted with the date of patient enrollment as an additional predictor. The size of the effect of the date of patient enrollment measures the extent to which outcomes have improved over time for reasons not explained by the available predictors (eg, as operators become more proficient with a device). A small effect is consistent with small-between-study variation and minimal susceptibility to unmeasured confounding variables.

Analyses were performed with SAS version 8.2 (SAS Institute, Cary, NC) and WinBUGS version 1.4 (MRC Biostatistics Unit, Cambridge, UK). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
The 30-day adverse event rate was 13.8% in the conventional guidewire arm (n=672) and 9.6% in the EPD arm (n=3286). Baseline clinical, angiographic, and procedural characteristics of the study population are displayed in Table 2.

Univariable Predictors of MACE
Univariable predictors of increased risk of 30-day MACE included current smoking; history of MI; glycoprotein IIb/IIIa inhibitor use; presence of thrombus; and increasing lesion length, RVD, SVG degeneration score, and plaque volume (Table 3). The presence of diabetes and use of an EPD were associated with a decreased risk of MACE (Table 3). Correlations were observed between the estimated plaque volume variable and the angiographic variables from which this variable is derived (lesion length, \( r = 0.83 \); RVD, \( r = 0.56 \)) and between SVG degeneration score and lesion length (\( r = 0.33 \)) and SVG degeneration score and estimated plaque volume (\( r = 0.33 \)). The remaining correlations between the candidate univariable predictors were low.
Treatment Effects
The probability of 30-day MACE increased according to the SVG degeneration score (Figure 3) and the quartile of estimated plaque volume (Figure 4) for both the conventional guidewire only and the EPD arms. There was a preserved 25% to 40% reduction in 30-day MACE associated with the use of an EPD compared with no protection across the range of baseline risk represented by these angiographic variables.

Multivariable Predictors of MACE
Logistic regression modeling was used to identify independent predictors of 30-day MACE, with adjustment for study and device-dependent effects. The strongest independent predictors were SVG degeneration score \((P<0.0001)\) and estimated plaque volume \((P<0.0001)\). Angiographic evidence of thrombus \((P=0.005)\), increasing patient age \((P=0.005)\), glycoprotein IIb/IIIa inhibitor use \((P=0.02)\), and current smoking \((P=0.03)\) also were independent predictors of adverse outcome (Table 4). Substitution of the estimated plaque volume variable with its component variables—RVD, MLD, lesion length, \((RVD)^2\), and \((MLD)^2\)—did not significantly improve model fit. Removal of actual glycoprotein IIb/IIIa inhibitor use from the multivariable model did not significantly alter the effect estimates of the remaining predictors or model fit (c statistic \(0.71\)).

No significant interaction was found between use of an EPD and use of a glycoprotein IIb/IIIa inhibitor either overall or by device type. There was no significant interaction between EPD use overall and angiographic measures (SVG degeneration score, \(P=0.95\); estimated plaque volume, \(P=0.31\)), suggesting preserved treatment benefit across these categories of risk. Including the date of enrollment also failed to significantly improve model fit \((P=0.31)\), suggesting consistency over time.

Figure 3. Unadjusted MACE at 30 days according to EPD use and SVG degeneration score. Absolute risk of MACE increases with increasing SVG degeneration score \((P<0.0001)\), but a relative treatment benefit is maintained across all categories of risk (interaction \(P=0.95\)). Only FDA-approved devices are included for the EPD arm of this analysis. RR indicates risk reduction.
Multivariable Predictors of Glycoprotein IIb/IIIa Inhibitor Use

In multivariable models, predictors of planned and actual glycoprotein IIb/IIIa inhibitor use were identical and included younger age (P < 0.0001), increasing estimated plaque volume (P = 0.0002), and presence of thrombus (P = 0.006). These findings suggest that glycoprotein IIb/IIIa inhibitors were selected and used in an angiographically higher-risk patient population.

Effect of Vessel Predilation

Predilation before EPD placement or stenting was reported in some of the included studies. Before EPD deployment, it was performed infrequently, with rates ranging from 4.5% in the SAFER trial to 14.5% in the BLAZE II registry. Subsequent predilation before stenting was performed slightly more frequently, with an overall frequency ranging from 16.1% in the FIRE trial to 32.8% in the Proximal Protection During Saphenous Vein Graft Intervention Using the Proxis Embolic Protection System (PROXIMAL) trial. A sensitivity analysis adjusting for predilation showed preserved treatment benefit of EPD use.

Between-Trial Variation

The posterior distribution of the interstudy correlation coefficient was concentrated on values < 0.05 (mean, 0.0104) with 98.8% of its density < 0.1, implying that there is little unexplained variation between studies. As a measure of the sensitivity of the model, we estimated that a change equal to 2 times the between-study variance component would translate to an absolute change in the predicted probability of MACE of only 0.8%.

Discussion

SVG PCI is associated with a high risk of MACE, mainly periprocedural MI, resulting predominantly from distal embolization of atherosclerotic plaque and friable debris within the graft, causing microvascular occlusion and no reflow.19–23 These acute procedural complications confer a poor long-term clinical outcome.6,24,25 The ability of EPDs to capture debris liberated during SVG PCI has been supported by analysis of aspirated debris from retrieved filters,26 and the roughly 40% reduction in MACE associated with their use strongly supports the concept that atheroembolization plays a causative role in the development of MACE during SVG PCI. Yet, the use of these devices in SVG PCI is not universal because of device complexities and belief on the part of some operators that certain lesions (eg, “discrete” or “smooth” in appearance) may carry sufficiently low risk to obviate the added time and expense of EPD use.

Most prior analyses evaluating predictors of adverse events in SVG PCI have been limited predominantly by their small size, retrospective nature, and performance before the concomitant use of stents and glycoprotein IIb/IIIa inhibitors.27–32 These studies implicated increasing graft age and angiographic characteristics such as presence of thrombus, lesion length, and diffuseness of disease as predictive of adverse events. The most recent studies of late (1 to 3 years) outcomes for patients undergoing SVG PCI are retrospective, span a period of time when therapies were evolving (1990 to 1998), and are contradictory regarding conclusions relating event-free survival and stenting.4,33

Since 2002, > 4000 patients have been enrolled in studies evaluating EPDs.7–11,15 The rates of adverse events in the active treatment arms have ranged from 3.8% to 11.6% within studies designed to evaluate new EPDs for FDA approval.34 This wide variation begs the question of the relative roles of patient and lesion characteristics, device improvement, and refinement of operator technique on the
probability of MACE within any given study or patient population.

We previously performed an analysis of predictors of short-term (30-day) adverse events after SVG PCI based on patients enrolled in the SAFER trial. Two novel variables (SVG degeneration score and estimated lesion plaque volume) were identified as being more powerful than classic clinical and angiographic features. Since the completion of the SAFER trial 5 years ago, however, >3000 additional patients have been enrolled in studies of new EPDs. There has been substantial variability of reported MACE rates across these studies. Anecdotally, this variation has been attributed to changes in inclusion characteristics or the efficacy of devices, but such hypotheses have not been formally tested.

We sought to determine predictors of 30-day MACE in this larger body of data to validate the previously identified angiographic predictors of MACE, to identify additional predictors, and to establish the reliability of an inclusive model to predict MACE. In the present analysis of nearly 4000 patients enrolled in embolic protection studies, we confirmed the independent predictive value of the 2 novel angiographic measures of plaque burden for 30-day MACE. We also identified additional independent predictors (patient age, glycoprotein IIb/IIIa inhibitor use, current smoking, and presence of thrombus). Finally, we confirmed that this angiographic and clinical model explains variation in MACE probability for individual subjects with a high degree of accuracy (c statistic=0.71) and can accurately predict MACE rates in studies with little remaining between-study variability, suggesting that the effects of unmeasured confounders are minor.

**Plaque Burden Measures Predict MACE After SVG PCI**

We found that simple estimators of volume and linear extent of disease burden are the most highly predictive factors accounting for adverse 30-day outcomes. Because major adverse cardiac events after SVG PCI occur in the setting of atheroembolism and because such events are reduced significantly when atheroemboli are prevented by effective retrieval devices, it is logical that the magnitude of plaque burden would correlate with the risk of embolization and resultant adverse events when that plaque is manipulated by stent expansion. This finding is important for estimating individual patient risk given that the absolute risk without embolic protection varies from 6.5% to 35.5%. The treatment benefit conferred by use of an EPD was preserved across all categories of risk, a finding that supports their use across all SVG PCIs represented in these trials. Furthermore, cost-effectiveness analysis has supported their use in eligible patient populations. It is important to note, however, that the safety and efficacy of EPDs in SVG PCI have not been evaluated in certain populations excluded from enrollment (ostial lesions, total occlusions, in-stent restenosis, anastomotic lesions).

**Is Glycoprotein IIb/IIIa Inhibitor Use Associated With MACE?**

Studies evaluating glycoprotein IIb/IIIa inhibitors in SVG PCI have suggested that these agents generally are not protective against adverse events. Most analyses suggest that glycoprotein IIb/IIIa inhibitors have been associated with increased MACE rates, with only isolated studies suggesting potential benefit. We found glycoprotein IIb/IIIa inhibitor use to be associated with a higher rate of adverse events independently of the objective angiographic predictors and not associated with device-specific benefits. Because the use of glycoprotein IIb/IIIa inhibitors was not randomized in these studies, however, one cannot attribute a protective or detrimental effect to these agents. Our analysis would indicate that these medications were chosen by operators for use in patients with higher perceived risk of MACE.

**Effect of Diabetes**

Diabetic patients were well represented in this cohort, making up almost 40% of the data set. The presence of diabetes appeared to be protective after SVG PCI in univariable but not multivariable models, a paradoxical finding because diabetes generally is associated with a higher risk of adverse events after coronary PCI. Diabetic patients were significantly younger, had lower SVG degeneration scores, and had smaller estimated plaque volumes, which may account for their lower event rate in this data set.

**Study Limitations**

Our findings should be considered within the context of our study design. In studies of EPDs, reported 30-day MACE are composed predominantly of periprocedural MI. Although we did not have access to later (1-year) clinical event rates in this pooled data set, evidence suggests that periprocedural MI is predictive of late mortality in SVG PCI. We combined studies with similar inclusion and exclusion criteria that were either randomized trials or registries. Analysis without inclusion of the single registry did not alter the effect estimates of the model.

**Trial Design Implications of an Explanatory Model of MACE in SVG PCI**

Our analysis confirms consistent benefits for the use of approved EPDs across risk strata. Despite these observations, however, the use of EPDs for SVG PCI is not universal in clinical practice, in part because of the additional complexity related to the use of these devices during the procedure. The development and evaluation of newer devices that have reduced crossing profiles or other features that increase their ease of use have clinical importance. Each new device, however, has been required to show noninferiority compared with an active control arm in relatively large (≈800 patient) randomized trials. Although “outcome drift” is often a concern in sequential noninferiority studies, in the case of EPD trials, the unadjusted rates of MACE have, if anything, “drifted” downward over time, further increasing the sample sizes required to demonstrate noninferiority. In the case of bare metal stents, once the patient- and lesion-specific predictors of procedural success and restenosis were identified from individual trials, the large body of available clinical trial data was compiled to establish methods for nonrandomized (ie, Bayesian) evaluation of new bare metal stents. In general, the implementation of such methods depends on the...
completeness of the explanatory model for the outcomes of interest and negligible effects of between-study variation.

We found that the range of expected MACE rates, as observed across embolic device studies and in our model, ranged by >6-fold across risk categories. This variation, however, was almost completely explained by clinical and angiographic predictors, the effects of which we have quantified. After adjustment for these variables, the amount of remaining variation among studies was relatively small, significantly <10% of the total variation between observations. In terms of predicted rates, this translated to a 95% confidence interval of <1% variability in terms of absolute MACE after application of the covariate adjustment models. Furthermore, the independent effects of time (as might be attributed to unmeasured confounders over time such as improved devices or operator technique) were not significant across the included studies. Therefore, it may now be possible to consider the use of covariate-adjusted historical performance data as an objective benchmark for the evaluation of novel devices in this arena. The reliability of this model suggests that new EPD safety and efficacy could be evaluated in the future compared with risk-adjusted models of expected rates of adverse events. Such trials could be designed to demonstrate noninferiority to already-approved EPDs.

This patient-level analysis of 3958 individuals undergoing SVG stenting across 5 randomized trials and 1 registry supports the power of 2 novel angiographic variables (graft degeneration and estimated lesion plaque volume) to predict adverse events with and without the use of EPD. Future evaluation of new EPDs may be expedited by knowledge of the effect of these potent predictors. In addition, this analysis confirms the roughly 40% treatment effect of EPD in reducing MACE compared with conventional guidewire use across the range of baseline risk.

Disclosures

Dr Baim is an employee of Boston Scientific. Dr Kuntz is an employee of Medtronic. Dr Popma has received research grants from Boston Scientific and Josted Medicor. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Saphenous vein graft percutaneous coronary intervention carries with it a high risk of major adverse cardiac events, particularly periprocedural myocardial infarction. The short-term risk approaches 20%, and before the introduction of embolic protection devices, no adjunctive therapy had been shown to reduce this risk. Despite accumulating evidence from randomized trials suggesting consistent reductions in the rate of 30-day major adverse cardiac events with the use of embolic protection devices by ≈40%, it is estimated that these devices are used in only half of saphenous vein graft interventions. Our analysis, which pooled 3958 patients enrolled in 5 randomized, controlled trials and 1 registry of embolic protection devices, identified 2 angiographic measures of plaque burden, plaque volume and a graft degeneration score, as the most important independent predictors of 30-day major adverse cardiac events. Additional independent clinical risk factors included increasing patient age and tobacco use. Saphenous vein graft percutaneous coronary intervention consistently provided embolic protection in reducing 30-day major adverse cardiac events across the broad range of characteristics in patients tested in randomized trials. The reliability of the model developed across patients and trials suggests that new embolic protection device safety and efficacy could be evaluated in the future against risk-adjusted models of expected rates of adverse events. This could facilitate evaluation of new embolic protection devices and their adoption to prevent adverse events.